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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,556	11/19/2003	Swen Holder	03806.0590-00	5066

22852 7590 09/14/2006

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EXAMINER	
HABTE, KAHSAY	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/715,556	HOLDER ET AL.	
	Examiner	Art Unit	
	Kahsay Habte	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-28 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-28 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-28 are pending in this application.

Response to Amendment

2. Applicant's amendment filed 8/04/2006 in response to the previous Office Action (3/27/2006) is acknowledged. Rejection of claims 1-28, under 35 U.S.C. § 112, first paragraph (items 5-6) has been maintained. The obviousness double patenting rejection (items 3-4) has been obviated.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The new proviso recited in claims 1, 9 i.e. "(2) the compound is not 3-{4-(3,4,5-trimethoxyaniinocarbonyl)-3-oxo-2,3-dihydropyridazine.....(3) when A is NHCOCH(CH3)2, Ar is not unsubstituted or at least monosubstituted bicyclic heteroaryl" is lacks description. Even a negative limitation requires description, *Ex Parte Grasselli,* 231 USPQ 393.

Response to arguments

Applicant's argument filed 8/04/2006 has been fully considered but it is not persuasive.

Applicants argue, "The compounds of formula (I), as described in the originally-files specification include the compounds that were 'provisoed out' in provisos (2) and (3), i.e.,....., and compounds when A is $NHCOCH(CH_3)_2$, Ar is unsubstituted or at least monosubstituted bicyclic heteroaryl. A limitation excusing species of a genus is sufficiently supported by an original specification that taught the entire genus, because the 'specification, having described the whole, necessarily described the part remaining,' as well as part being provisoed out. See *In re Johnson*, 194 USPQ 187, 196 (CCPA 1977)". The examiner disagrees with applicants. Applicants' analysis of the law is not agreed with. In *Ex Parte Grasselli*, applicants sought to avoid a 35 USC 102(b) anticipation by writing a proviso which excluded the prior art species, which proviso lacked any description. By contrast, in *In re Johnson*, 194 USPQ 187, 196, the fact situation was somewhat different. There, the claims were narrowed to avoid material lost in an interference. Since the fact situation here is the same as *Ex Parte Grasselli*, and different from *In re Johnson*, the former, and not the latter will be followed. The vast majority of amendments are tendered without use of proviso.

Applicants are reciting a proviso to overcome prior art rejections that were not originally part of the disclosure. For example, the condition in proviso (3) "when A is $NHCOCH(CH_3)_2$, Ar is not unsubstituted or at least monosubstituted bicyclic heteroaryl"

requires that Ar to be substituted when A is $NHCOCH(CH_3)_2$ is a new concept. There is no written description for this proviso. Applicants are reciting negative provisos to overcome a prior art rejection. It is recommended that applicants overcome prior art rejection by deleting substituents from formula (I).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In claim 9, it is recited a method of inhibiting CDK2 *in vivo* and in claims 17-24, it is recited a method of treating cancer in general but the specification is not enabled for such a scope.

A number of factors are relevant to whether undue experimentation would be required to practice the claimed invention, including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the

art, and (8) the breadth of the claims." In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

(1). Breadth of Claims: Claims 9-25 are directed to a method for inhibiting CDK2 *in vivo* and a method for treating a patient suffering from cancer that comprises inhibiting cancer cells by administering a physiologically active amount of a compound of formula (I).

a. Scope of use - The scope of use that applicants intend to claim is very broad. To this day, it is impossible to treat all cancer cells with a single pharmaceutical drug. Please see below for the explanations that cancer cells are broad and different one from the other. Cancer cells can exist in different parts of the body and the nature of these cancer cells differs one from the other. For example, the treatment of bone cancer cannot be the same as the treatment of skin cancer. The drug that inhibits bone cancer cells may require more doses than the cancer cells in skin. The form of delivery for both said cancers (radiation, ointment, tablets, etc.) is not the same. For instance, one has to get deep to the bones to inhibit the cancer cells in the bones, while applying the drug on the surface of the skin can inhibit cancer cells on skin. It is also a fact that some cancer cells need more drugs than the others. It is also true that the compounds could be having antagonistic effect or agonistic effect when administered to the body. Which diseases (cancer cells) are inhibited by the administration of the drug and which are

not? Applicants claim that all cancer cells can be treated by single pharmaceutical drugs, thus is not enabled.

It can be shown that cancer cells in general are extraordinarily broad. For a compound or genus to be effective against cancer cells generally is contrary to medical science. Cancer is a disease, which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate cancer. There is no common mechanism by which all, or even most, cancers arise. Accordingly, treatments for a cancer or inhibition of cancer cells are normally tailored to the particular type of cancer cells present, as there is no, and there can be no "magic bullet" against cancer cells generally.

Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities.

b. Scope of Compounds - The scope of the compounds is also broad. It is apparent that hundreds of millions of combinations of compounds can be created from the definitions, owing especially to broad scope of A, A1, A2, R, R1 and R2.

(2). Direction of Guidance: Applicants indicate that their compounds can be used for the inhibition of the kinase CDK2 and also disclose that CDK2 is usually part of a complex, such as CDK2/cyclin A or CDK2/cyclin E complexes. The amount of direction or guidance is minimal. There is no guidance for the treatment or inhibiting cancer cells in general. As the rejection states, there is no enablement for the treatment of cancer in general. It is also noted that generic dosage is disclosed, regardless of the nature of the cancer cells.

(3). State of Prior Art: There is no evidence of record that compounds structurally similar to these pyridazinone derivative compounds of formula (I) or indeed are in use for the treatment of cancer in general, or anything remotely close to cancer in general.

(4). Working Examples: Test procedures and assays are provided in the specification at page110 only for 37 compounds and it is concluded that the representative compounds of formula (I) demonstrated positive inhibitory activity with IC_{50} ranging from 0.012 μM to 0.905 μM, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders embraced the instant claims. The disorders encompassed by the instant claims (i.e.

cancer in general), some of which have been proven to be extremely difficult to treat. Note that it is unclear if the compounds that are not tested failed or pass the test.

(5). Nature of the Invention and Predictability: The invention is directed to inhibiting cancer cells in general. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Cancers are especially unpredictable due to their complex nature. Please refer to the earlier rejection in item 2 that shows different types of cancers. The treatment of one type of cancer could not be necessarily the same for the other type. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

(6). The Quantity of Experimentation Necessary: Immense, because so many cancerous cells are covered; see part (1).

(7). The Relative Skill of Those in the Art: The relative skill is extremely very low. To this day, there is no magic bullet that can treat cancer cells in general.

Response to arguments

Applicant's argument filed 8/04/2006 has been fully considered but it is not persuasive.

Applicants indicate that have amended the claim from "any patient" to "*in vivo*" to advance prosecution. There is no *in vivo* experiment at page 110-112. Applicants have submitted a declaration under 1.132 (Eric Parmantier) and recent article (Cancer Research, 66(8), 2006, pages 4299-4308) to support their argument. A declaration is under 1.132 is used to overcome an obviousness rejection. The declaration or the article submitted by applicants does not link the inhibition of CDK2 to the treatment of cancer in general. Applicant's disclosure at pages 110-111 show the inhibition of CDK2, but there is no correlation between the inhibition and the treatment of cancer in general.

According to the article (Cancer Research, 66(8), 2006, page 4308, second column, second paragraph), "The precise mechanism determining tumor cell fate after treatment with CDK inhibitors still remains elusive, gaining a better understanding of the survival and checkpoint adaptations will help elucidate the underlying factors regulating the phenotype response." This shows that the study is at its early stage and that further studies are needed to understand the underlying mechanism of CDK2. Note that the disorder encompassed by the instant claims (i.e. cancer in general) is very broad. To this day, there is no magic bullet that can treat cancer in general. It is recommended that applicants delete these claims to overcome this rejection.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kahsay Habte
Primary Examiner
Art Unit 1624

KH
September 12, 2006